5-Fluorouracil Rechallenge After Cardiotoxicity

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
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Patient:	**Male, 66-year-old**
Final Diagnosis:	**Colon adenocarcinoma • ventricular arrhythmia**
Symptoms:	**Cardiac arrest • syncope**
Medication:	**—**
Clinical Procedure:	**Cardiac catheterization • Cardiac Electronic Implantable Device (CEID)**
Specialty:	**Cardiology • General and Internal Medicine • Oncology**

Objective:	**Unusual clinical course**
Background:	5-Fluorouracil (5-FU) is a widely used intravenous chemotherapy agent that is highly effective in the treatment of a variety of solid malignances. Cardiotoxicity related to 5-FU is a complex clinical entity associated with significant morbidity and mortality. Whether a patient who experienced a major cardiac side effect from 5-FU can be safely rechallenged with this drug is a clinical dilemma.
Case Report:	We present the case of a patient with stage III colorectal adenocarcinoma who experienced ventricular fibrillation during the first cycle of FOLFOX (5-FU, folinic acid, and oxaliplatin) regimen in the adjuvant setting. Post-resuscitation electrocardiogram revealed ST-elevation in the inferior leads with reciprocal changes. Coronary angiogram revealed no obstructive coronary artery disease. Cardiac workup led to the conclusion of probable fluorouracil-induced vasospasm as the cause of his cardiac arrest. He received implantable cardioverter defibrillator. The decision was made to hold 5-FU. At 3-month follow-up, there was evidence of progressive metastasis. After comprehensive risk-benefit discussions, the decision was made for palliative chemotherapy using 5-FU/leucovorin. A pre-treatment regimen including isosorbide dinitrate, diltiazem, and metoprolol was used. The patient tolerated 5-FU rechallenge without recurrent cardiovascular complication.
Conclusions:	The cardiotoxicity profile of 5-FU can range from anginal chest pain to sudden cardiac death. When considering 5-FU rechallenge, clinicians should adopt a multidisciplinary approach, favor using prophylactic antianginal therapy, change to bolus dosing, and use continuous telemetry monitoring. Screening patients for dihydropyrimidine dehydrogenase deficiency prior to 5-FU administration may facilitate an individualized strategy for optimal dosing and safety.
MeSH Keywords:	**Cardiotoxins • Coronary Vasospasm • Dihydropyrimidine Dehydrogenase Deficiency • Fluorouracil**
Full-text PDF:	https://www.amjcaserep.com/abstract/index/idArt/924446

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Background

Cardiovascular disease and cancer are the 2 leading causes of death and disability in the United States and worldwide [1,2]. According to the World Health Organization, cancer incidence is expected to increase by 70% over the next 20 years, and more than half of cancer patients will live at least a decade, often coincident with multiple non-malignant comorbidities [3]. Among these, cardiovascular disease is one of the most important determinants of morbidity and mortality in cancer survivors [4]. There is an unmet medical need to better understand the intersection of cancer and heart disease.

5-Fluorouracil (5-FU) is the third most commonly used intravenous chemotherapeutic agent in the treatment of solid malignancies, including colorectal, pancreatic, bladder, breast, and head and neck cancers [5]. It is the most important component of adjuvant chemotherapy for colorectal cancer and is used as FOLFIRI (5-FU, folinic acid, and irinotecan) [6] or FOLFOX (5-FU, folinic acid, and oxaliplatin) regimens [7]. 5-FU can cause adverse effects ranging from mild gastrointestinal symptoms to severe neutropenia and life-threatening cardiovascular events. The incidence of cardiotoxicity has been reported to range from 1.5–18% [8]. Whether a patient who experienced a major cardiac side effect from 5-FU can be safely rechallenged with this drug is a clinical dilemma [9]. There have been only a few case reports and case series of successful rechallenge with 5-FU in the literature [10]. We present the case of a patient who was successfully rechallenged with 5-FU along with a pre-treatment regimen including isosorbide dinitrate, diltiazem, and metoprolol. The patient tolerated the treatment well without recurrent cardiovascular complication.

Case Report

A 66-year-old Caucasian male with a past medical history of chronic heart failure with preserved ejection fraction (NYHA Class III), hypertension, transient ischemic attack, peripheral vascular disease, and persistent atrial fibrillation (CHA$_2$DS$_2$-VASc score of 6) and venous thromboembolism on Xarelto (rivaroxaban) was diagnosed with clinical stage III colorectal adenocarcinoma with obstructing mass in the distal ascending colon. He underwent a subtotal colectomy and end ileostomy. Pathology revealed moderately differentiated adenocarcinoma (4×4×1.6 cm) invading through the muscularis propria into the peri-colonic tissue with peri-neural invasion and 1 out of 22 lymph nodes with metastatic cancer. He was subsequently planned for treatment with FOLFOX regimen in the adjuvant setting.

During the first cycle of chemotherapy, the patient suddenly collapsed during the infusion. Telemetry revealed ventricular fibrillation (VF), and he was immediately defibrillated (Figure 1A). He received 1 round of cardiopulmonary resuscitation (CPR) and 2 rounds of direct cardioversion before being successfully resuscitated. Electrocardiogram (ECG) immediately after the return of spontaneous circulation revealed atrial fibrillation, ST-elevation in the inferior leads with reciprocal ST-depression in the lateral leads (Figure 1B). The patient complained of lightheadedness and diaphoresis but denied chest pain, shortness of breath, palpitations, nausea or vomiting. He was a never smoker with no alcohol or recreational drug use. Family history was negative for premature coronary artery disease or sudden cardiac death. Apart from his chemotherapy regimen of FU, oxaliplatin, palonosetron, leucovorin, and dexamethasone, his home medications included rivaroxaban 20 mg by mouth once a day, pravastatin 20 mg by mouth once a day, ondansetron 8 mg by mouth every 8 hours as needed for nausea or vomiting and ferrous sulfate 325 mg by mouth daily. He underwent an emergent cardiac catheterization.

Vital signs in the cardiac catheterization laboratory were notable for hypotension with a systolic blood pressure of 70 mmHg; his blood pressure improved to 101/61 mmHg with dopamine infusion at 10 mcg/kg/min. His heart rate was 74 beats/min, respiratory rate was 24 breaths/min with oxygen saturation of 94%, and he was afebrile. Cardiopulmonary physical examination was remarkable for an irregularly irregular heart rhythm, normal S1 and S2 without murmurs, rubs, or gallops. He had no jugular venous distention, and his chest was clear to auscultation without rales. He had 2+ pulses throughout, and his neurological examination revealed no focal deficits. Initial laboratory testing showed mild leukopenia with a white blood cell (WBC) count of 3.6×10^3/μL, anemia with a hemoglobin of 7.4 g/dL and hematocrit of 23.2, and platelets of 233×10^3/μL. Basic metabolic panel revealed sodium 127 mmol/L, potassium 3.7 mmol/L, bicarbonate 19 mmol/L, glucose 142 mg/dL, blood urea nitrogen (BUN) 26 mg/dL, creatinine 0.8 mg/dL and an estimated glomerular filtration rate (eGFR) of 93.1 mL/min/1.73 m^2. His troponin I was elevated at 1.42 ng/mL (reference range: <0.04 ng/mL) and brain natriuretic peptide (BNP) was 370 pg/mL (reference range: <100 pg/mL). He had an oral glucose tolerance test (OGTT) 4 months prior which was normal. HbA1C was never checked on this patient, possibly because it can be affected by his chronic iron deficiency anemia [11].

Coronary angiogram revealed no evidence of thrombo-occlusive coronary artery disease (Figure 2A–2D). Left ventriculogram while on dopamine demonstrated normal left ventricular systolic function. Right heart catheterization revealed right atrial pressure of 3 mmHg, pulmonary artery pressure of 21/6 mmHg, and pulmonary capillary wedge pressure of 6 mmHg. By using pulmonary artery saturation of 79.6% and
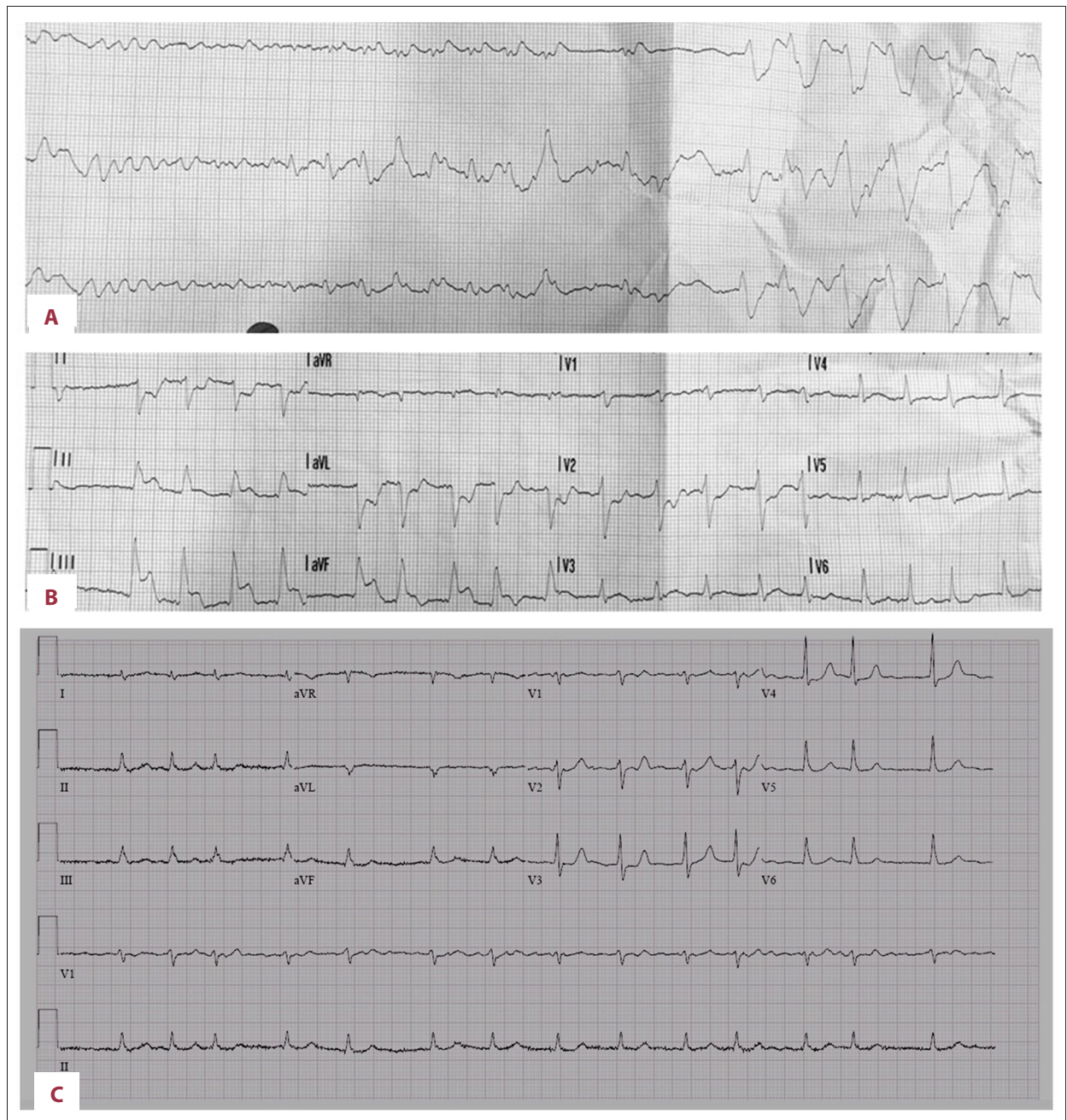
Figure 1. (**A**) ECG strip showing ventricular fibrillation converting to monomorphic ventricular tachycardia after DC cardioversion. (**B**) 12-Lead ECG showing ST-elevation in the inferior leads with reciprocal ST-depression. (**C**) 12-Lead ECG showing atrial fibrillation with nonspecific ST-T changes.

aortic saturation of 98.9%, calculated cardiac output by Fick's equation was 14.4 L/min with a cardiac index of 6.4 L/min/m². Pulmonary vascular resistance was calculated at 1.1 Woods unit. Transthoracic echocardiogram showed left ventricular ejection fraction (LVEF) of 55–65% with mild inferior wall hypokinesis, grade 1 diastolic dysfunction, and no valvular abnormalities. Based on these findings, it was felt that the patient's cardiac arrest and ST-elevation was likely due to fluorouracil-induced vasospasm. His low filling pressures indicated volume depletion, and echocardiogram showed a hyperdynamic right ventricle in the setting of hypovolemic state and inotropic effect. The patient was transferred to the CCU where he received intravenous fluids. An ECG performed 30 minutes after cardiac catheterization showed a complete resolution of ST-T abnormalities (Figure 1C). Blood pressure improved to 110/70 mmHg, and he was weaned off dopamine in 24 hours. His serial troponin I
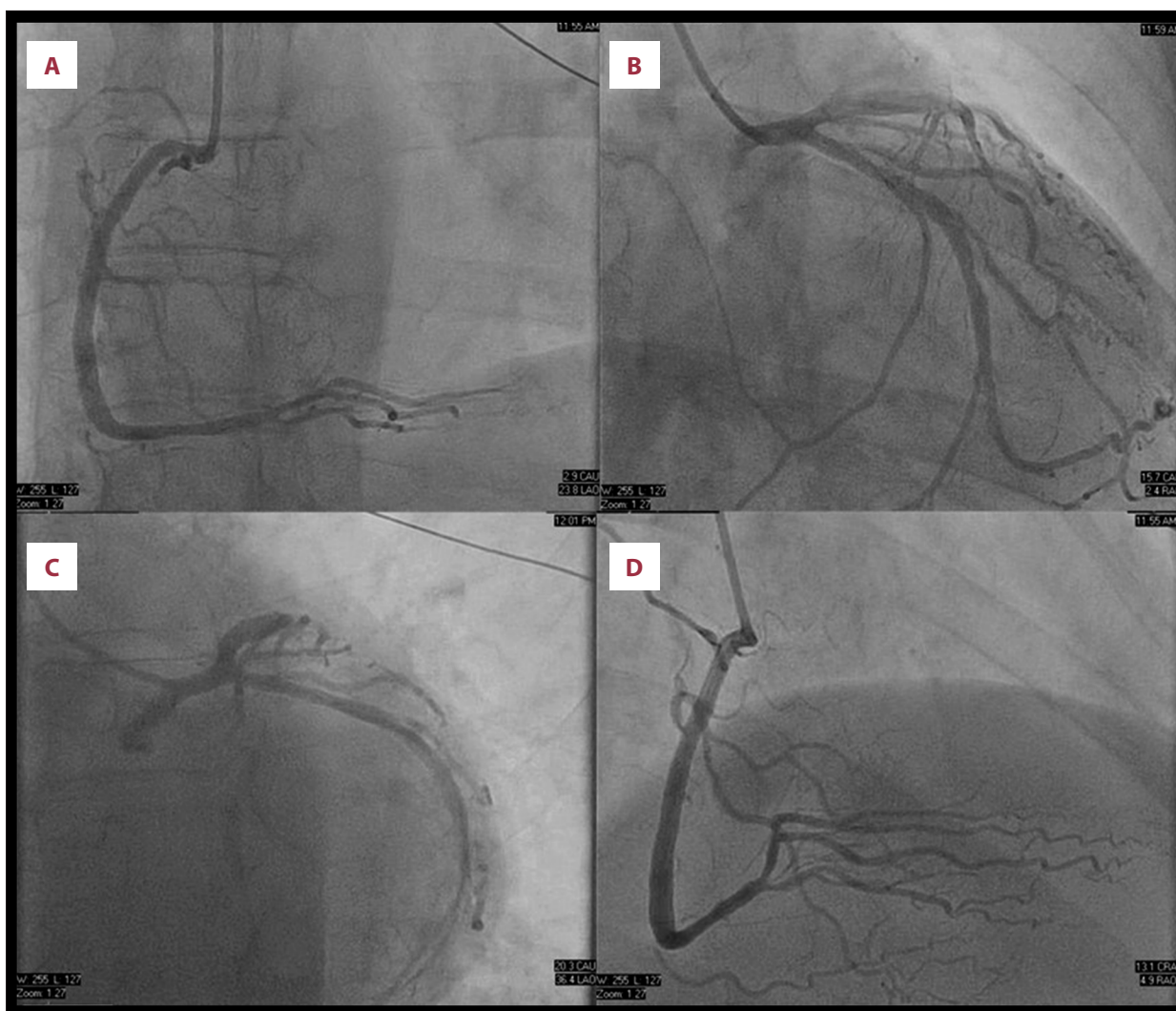
Figure 2. (**A–D**) Cardiac catheterization showing clean coronary arteries with no evidence of significant atherosclerosis.

down-trended to 0.19 ng/mL, and he remained asymptomatic and hemodynamically stable.

He was evaluated by cardiac electrophysiology the following day and underwent successful implantation of a single-chamber implantable cardioverter defibrillator (ICD) without complication. After extensive discussion among the patient, his family, oncology and cardiology teams, the decision was made to hold further cancer treatment with 5-FU. It was felt that the risk of recurrent cardiac events outweighed the potential benefit of preventing cancer recurrence. At a 3-month follow-up, a rising carcinoembryonic antigen (CEA) level prompted repeat imaging with computed tomography (CT) scan of the chest, abdomen, and pelvis which revealed metastatic disease involving the liver, peritoneum, left posterior pararenal fascia, mesentery, and possible abdominal wall. A month later, another CT scan demonstrated worsening liver metastasis, unchanged scattered peritoneal implants, and pelvic lymphadenopathy. Given

the worsening metastasis, oncology felt that chemotherapy with 5-FU would be the most efficacious treatment to slow his disease progression without any other realistic options. The patient expressed that he would like to try any available option accepting all the risks and benefits. The decision was made to proceed with additional palliative chemotherapy using 5-FU/leucovorin to be delivered in the inpatient setting while on continuous telemetry due to his prior history of cardiac arrest. Cardiac workup prior to rechallenge with 5-FU revealed a normal troponin I level (0.02 ng/mL), the ECG showed atrial fibrillation with nonspecific ST-T changes, and repeat echocardiogram was unchanged with normal LVEF.

The patient was premedicated with isosorbide mononitrate 30 mg by mouth daily, metoprolol succinate 25 mg my mouth daily and diltiazem extended-release 120 mg by mouth daily. He received 5-FU infusion while on continuous telemetry. He tolerated the chemotherapy infusion well without any symptoms.

On telemetry, one 8-beat non-sustained ventricular tachycardia (VT) was noted without symptoms. The patient completed his chemotherapy and was observed for 48 hours afterward without any immediate or major complications. Thereafter, he continued palliative 5-FU chemotherapy for four more months before succumbing to colon cancer.

Discussion

The most commonly documented cardiovascular side effect of 5-FU is chest pain with or without associated ECG changes [12]. 5-FU cardiotoxicity profile also includes cardiac arrhythmias, angina/myocardial infarction, ventricular dysfunction, cardiogenic shock, cardiac arrest, and sudden cardiac death. Cardiovascular mortality rates are reported to range from 0% to 8% [13]. The proposed mechanisms of 5-FU cardiotoxicity include myocardial ischemia, coronary vasospasm, and toxic myocarditis. Among these mechanisms, coronary vasospasm is the most reported [14]. A study demonstrated that 50% of patients developed vasospasm of the brachial artery after administration of 5-FU, while patients who received non-5-FU chemotherapy did not experience vasospasm [15]. Drug-induced coronary vasospasm has also been demonstrated in coronary angiography [16]. 5-FU may also act on the kallikrein-thrombin pathway, which leads to increased concentrations of micro-thrombi. Concomitant leucovorin administration increases the risk of 5-FU cardiotoxicity. Finally, 5-FU administration can cause irritability and anxiety leading to sympathetic overactivation, which can trigger the development of tachycardia-induced cardiomyopathy.

Reintroduction of 5-FU following cardiotoxicity has long been a clinical dilemma. A retrospective study of 377 patients documented a mortality of 13% with 5-FU rechallenge [17]. In another study, 18 out of 20 patients rechallenged with 5-FU following cardiac side effects experienced major adverse cardiac events, including 3 myocardial infarctions and 2 deaths [18]. In a case series of 11 patients, all the patients with suspected 5-FU-induced coronary vasospasm were successfully rechallenged and went on to complete chemotherapy following pre-treatment with 2 calcium channel blockers (long-acting nifedipine and short-acting diltiazem) and a long-acting nitrate (isosorbide dinitrate) for cardioprotection in conjunction with close telemetry monitoring [10]. These patients received anti-spasm medications at least 24 hours before, during, and 24 hours after rechallenge. With this pre- and post-treatment regimen, all patients were able to complete multiple cycles of 5-FU rechallenge without recurrent chest pain or another cardiac complication. Alternative strategies for rechallenge include dose reduction and switching from infusion to bolus administration [19].

Moreover, every patient should have a thorough cardiac history taken and a baseline ECG prior to rechallenge, which can be used for comparison during reintroduction of the drug. In one study, patients on 5-FU were closely monitored on telemetry before and during 5-FU infusion. The authors showed that 24% of patients had asymptomatic ST-segment changes before infusion, which increased to 68% during infusion, revealing that the incidence of ischemic episodes significantly escalated during the infusion. The more recently described "Tei Index", or the myocardial performance index on echocardiography [20], has been shown to identify subclinical or occult cardiotoxicity in patients receiving 5-FU. Thus, ECG monitoring and the Tei index may be useful in identifying those patients who would be at an increased risk of cardiotoxicity from 5-FU. Other studies that may be useful in better characterizing 5-FU-induced myocardial toxicity include cardiac magnetic resonance (CMR) which can detect subendocardial or transmural myocardial infarction by delayed enhancement imaging [21]. In our patient, CMR was not performed; thus, vasospasm-induced myocardial scarring cannot be definitively ruled out.

The risk factors for cardiotoxicity in patients receiving 5-FU remain incompletely understood. Certain pharmacologic and patient-related factors could lead to an elevated risk of cardiac side effects. One study showed that pre-existing cardiovascular disease and renal disease with a creatinine clearance of <30 mL/min were risk factors [22]. In a study with gastrointestinal malignancy patients, the incidence of cardiotoxicity was 8.5% in those receiving FOLFOX as continuous infusion and less than 3% in those receiving bolus administration, suggesting that the total duration of therapy may increase the risk of cardiotoxicity [14,23]. These factors should be taken into consideration before planning for drug rechallenge. Additionally, our patient had an elevated BNP, which has been shown to predict adverse cardiac events irrespective of LVEF [24]. The role of BNP in predicting 5-FU cardiotoxicity is an interesting area for future research. After percutaneous coronary intervention (PCI) for first ST-elevation myocardial infarction (STEMI), tight peri-procedural glycemic control in hyperglycemic patients has been associated with increased myocardial salvage [25]. Whether tight glycemic control has a role in mitigating cardiotoxicity from 5-FU is an area of future investigation. Before drug rechallenge, our patient's ICD was interrogated, and it demonstrated stable and satisfactory device parameters without evidence of arrhythmias. Absence of ventricular arrhythmias (VA) on device interrogation gave us an extra layer of comfort in proceeding with 5-FU rechallenge. The advantages of an ICD are not only the secondary prevention of sudden cardiac death but also providing us with additional prognostic parameters, such as atrial arrhythmia burden, non-sustained VT, and treated episodes of VT/VF. This information further helps to risk-stratify patients prior to reintroduction of potentially cardiotoxic drugs [26].

Newer studies from Europe have shown that 5-FU-related toxicities can be reduced by detecting patients with dihydropyrimidine dehydrogenase (DPD) deficiency and utilizing simple adaptive dosing strategy [27,28]. Underlying systemic inflammation has been found to play an important role in the pathogenesis and perpetuation of arrythmias through multiple direct and indirect mechanisms [29]. In a meta-analysis of 526 patients by Jiang and colleagues, it was found that patients with elevated baseline C-reactive protein (CRP) levels had increased AF recurrence after ablation [30]. Similarly, in a prospective study of 47 patients with ICD, the baseline and follow-up IL-6 levels at 9 months were elevated among patients with VA events compared to those without VA events [31]. Whether patients with DPD polymorphisms have higher levels of inflammation and whether their inflammatory status contributes to increased arrhythmogenesis are interesting areas for future research. Of note, there is evidence suggesting the clinical utility of anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and steroids in preventing atrial fibrillation recurrence after ablation [32]. The role of the newer cytokine blockers in preventing arrythmias is currently unknown, and studies are underway [33].

Conclusions

In conclusion, cardiotoxicity related to 5-FU is a complex clinical entity associated with significant morbidity and mortality.

Whether a patient who experienced a major cardiac side effect from 5-FU can be safely rechallenged with this drug is a clinical dilemma. If a second-line therapy is available, the general consensus is to opt for it. If alternative therapy is not available, rechallenge is considered and a comprehensive risk-benefit ratio must be defined. When considering 5-FU rechallenge, clinicians should adopt a multidisciplinary approach, favor using prophylactic anti-anginal therapy, and use continuous telemetry monitoring. Additionally, changing to bolus administration from continuous infusion has been found to be beneficial. In patients with a history of cardiotoxicity from 5-FU, ICD interrogation can provide information that identifies individuals who are at a high risk for developing recurrent VA from a potentially cardiotoxic cancer therapy. Employing genetic profiling to identify patients with polymorphisms in the metabolizing enzyme DPD before 5-FU administration has shown great promise and may facilitate an individualized strategy for optimal dosing and safety.

Department and Institution where work was done

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Conflicts of interest

None.

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